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Response to Docket No. FDA-2017-P-5396

This document comments on the Citizen's Petition requesting FDA should immediately seek removal of oral and transmucosal ultrahigh dosage unit (UHDU) opioid analgesics from the market.

We believe the petition should be denied because the scientific evidence upon which it relies is incomplete and the existing information has been misrepresented in the petition. Many of these concerns were identified and addressed by Coyle, et al.(1)

1. **The petition does not distinguish between opioid abusers and legitimate patients with pain. S**tudies to date alleging a dose threshold in mortality associated with prescription opioids have simply examined the daily prescribed dose of an opioid analgesic. They have not included other relevant features such as the motive of the person receiving the prescription. This line of research is still evolving, but it is clear that multiple groups exist (Green 2011, Kelly 2015): conflating these groups is likely to lead to errors of misattribution. Published evidence reveals that there are multiple remarkably different groups to consider:
    a. The legitimate patient
        i. The overwhelming majority of persons without risk factors who receive a prescription opioid for treatment of pain will use the drug as directed.
        ii. Substantial evidence and professional opinion indicates that this person is highly likely to use their prescription as prescribed and rarely develops substance abuse behaviors.
    b. The innocent bystander
        i. The innocent bystander refers to the person with few or no risk factors who develops a substance use disorder when treated appropriately for chronic pain. Less than 1% of legitimate patients who receive an opioid analgesic for treatment for a chronic pain condition will develop substance abuse behaviors (Fishbain 2008).
        ii. These patients often have or have had a history of alcohol, stimulant or other substance abuse problem before deciding to abuse an opioid. Routine brief screening instruments typically alert these concerns to the physician.
    c. The imposter (established opioid abuser)

i. A substantial portion of persons in this category are actually abusers posing as a patient in pain in order to use the health care system as a supplier of opioid analgesics for their abuse and dependence.
ii. These individuals masquerade as a legitimate patient, but never intended to use the drug as labeled for use. They intend to sell the drug or use themselves. By deceiving the prescriber, the use the health care system as their "dealer".

2. **Limiting the size of prescription dosage units is unlikely to meaningfully benefit any of these groups.**
    a. The legitimate patient
        i. A small proportion of legitimate patients have a condition that requires large daily doses. When this dosage is required, it should be administered in the smallest number of doses possible and as infrequently as possible in order to improve efficacy and reduce adverse events.
        ii. If the size of a dosage unit is decreased, these true patients will have to take many more tablets, which can be expected to cause increased rates of drug errors, adverse drug events and potentially increase the number of dosage units available for diversion. In addition, lowering available dosage sizes increases costs to both the patient and the health care system.
    b. The innocent bystander
        i. These patients have real pain, which should be treated in the most effective and safe manner.
        ii. If tablet size is decreased, we can expect increased rates of treatment failure, which could actually encourage the use of larger doses and the inevitable safety issues inherent in managing multiple tablet doses.
        iii. This group won't benefit from smaller dosage units because the issue is their desire to get high and the size of the dosage unit will not affect this desire.
        iv. Data indicate that the issue for this group is not the size of the dose, but the duration of treatment.
    c. The imposter (established opioid abuser)
        i. The imposter is often experienced at manipulating the health care system to obtain prescription opioids. The size of the dosage unit is less important to them. Indeed, as they become aware that smaller tablets create less suspicion, they will encourage prescribing of these dosage units so they appear like a legitimate patient.
        ii. Furthermore, if these individuals truly desire the drug, they can obtain opioid from myriad other sources, including heroin and illicitly manufactured fentanyl.

3. **The petition misinterprets the research literature**.
    a. The petition states that there is increased risk of overdose and death at a threshold of 90 morphine equivalents (MME)/day.
    b. The apparent threshold at 90 MME/day is likely an artifact due to underpowered analyses. In order to increase power, researchers have aggregated daily doses above a specified threshold. Therefore, an overdose event at 200 MME, 300

MME/day or even higher counts the same as an event at 90 MME/day. This produces the illusion of a dose threshold.

c. It is currently unknown whether a threshold exists. If such a threshold does exist, it is likely well above 90 MME/day because 90 MME/day is the lowest daily dosage typically included in the published analyses. However, the data are also consistent with much higher thresholds.
d. The biologic plausibility of a threshold seems unlikely. While it is logical to speculate that a higher daily dosage of an opioid would produce a higher rate of adverse events, this does not infer that a threshold exists. One would expect a legitimate patient to take their medication as prescribed. If their dose is increased, it is increased in a stepwise manner and the patient develops tolerance. One would not expect a sudden catastrophic event when an opioid is administered in this manner.
e. In contrast, sudden catastrophic events are expected among abusers of prescription opioids. In these cases, an abuser may take an unexpected amount of drug or, more likely, combine with other known or unknown toxic substances, including benzodiazepines, heroin and other drugs.
f. The multidrug use context of many substance use disorders and catastrophic events suggest that evidence is lacking for a prescription opioid threshold, and would be nearly impossible to detect because of the myriad doses and potential interactions between multiple substances, not to mention aberrant routes of administration like snorting and injecting, which lead to dramatic changes in absorption and toxicity.
g. The petition is also logically inconsistent in that it ignores transdermal formulations. The labeled dose of several fentanyl products are above the artificial threshold suggested. There is no justification presented for why transmucosal and solid oral formulations would be subject to the alleged dose threshold phenomenon when some of the citations also included fentanyl patches.
h. Coyle, et al., stated “The results of several reviewed studies show an increasing risk of misuse, overdose, and death with increasing opioid analgesic dose. However, these studies do not indicate that there is a specific dose that should not be exceeded for safe use, or that any dose below a specified threshold is safe. The available data support the conclusion that all opioid analgesic doses carry some level of risk, and that this risk increases continuously over a wide dose range.”

4. Conclusion
    a. Like many well intended but misguided interventions, the UHDU petition would penalize the legitimate patient and have little or no effect on abusers of the drug. The legitimate patient would experience more complicated and more expensive regimens to treat their pain. Increased complexity inevitably lead to therapeutic failure in some patients and increases the rate of adverse events.
    b. In contrast, there are essentially no benefits to the other groups – the abusers the ultimately are simply trying to obtain an opioid drug. These individuals do not care if they get a smaller dosage unit as witnessed by the switch for OxyContin 80 mg dosage units to Roxicodone 30 mg dosage units after OxyContin was reformulated.

c. Improved opioid prescribing for pain is an important goal that has life-altering implications for both chronic pain patients and substance abusers. Restrictions based on poor science have serious negative effects, including death.

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